

Economic Evaluation of Dupilumab for Moderate-to-Severe Atopic Dermatitis: A Cost-Utility Analysis

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ABSTRACT

Background. Moderate-to-severe atopic dermatitis can be difficult and costly to treat. The long-term health and economic outcomes of a new therapy, dupilumab, have yet to be evaluated. We aimed to identify the cost-effectiveness of dupilumab compared to usual care in moderate-to-severe atopic dermatitis.

Methods. We compared dupilumab to usual care with emollients for adults with moderate-to-severe atopic dermatitis inadequately controlled with topical therapy, or for whom topical therapies were medically inadvisable. Subpopulations of moderate and severe patients were examined separately. We used a lifetime Markov model from a US payer perspective with health states categorized by the percent decrease in Eczema Area and Severity Index (EASI) score after a patient began an intervention: at least a 50% decrease (EASI 50), 75% decrease (EASI 75), 90% decrease (EASI 90), or no response.

Results. The expected lifetime cost for patients treated with dupilumab was $509,600, including $267,800 in dupilumab drug costs and $241,800 in other healthcare costs. Average lifetime cost for usual care was $271,500. Dupilumab provided an additional 1.91 quality-adjusted life years (QALYs) over the remaining lifetime of a patient, leading to an incremental cost-effectiveness ratio (ICER) of $124,500. The ICER was lower for patients with severe atopic dermatitis ($95,800) than those with moderate atopic dermatitis ($160,000). Key drivers of the model were utility values for quality-of-life for non-responders, and the price of dupilumab.

Conclusions. This study was limited by data for health outcomes and costs over long time periods, particularly stratified by severity. We estimated that dupilumab improved health outcomes compared to usual care but with additional costs, with an ICER below commonly cited thresholds for cost-effectiveness. Dupilumab was projected to be more cost-effective in patients with severe atopic dermatitis, but even in patients with moderate atopic dermatitis, the ICER remained below the upper range of commonly cited thresholds.

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INTRODUCTION

Atopic dermatitis is a chronic skin condition causing itching, dry, and painful skin, that affects 11% of children and 3-7% of adults in the United States.[1-3] Atopic dermatitis can dramatically affect a patient's quality of life.[4] Itching often disrupts sleep leading to daytime drowsiness[5] and irritability, which can lead to psychological stress and impaired performance in school and at work. Additionally, aesthetic changes to visible skin can lead to social stress and isolation.[4]

Most patients with atopic dermatitis use bland moisturizers and emollients for treatment, along with meticulous and often difficult or lengthy skin care routines. Patients also focus on avoidance of triggers such as foods, products, or activities that increase their disease activity. Intermittently, patients use topical corticosteroids, and may implement long-term maintenance with a topical calcineurin inhibitor.[6] Unfortunately, over time, corticosteroid use may be associated with moderate or severe adverse events including adrenal suppression, telangiectasias, increased hair, skin tears, easy bruising, poor wound healing, acne and rosacea, and thinning/atrophic changes, which can be permanent.[7-9] Some patients may use phototherapy or systemic immunomodulatory agents, but few supportive data are available as to the efficacy of these therapies for atopic dermatitis.

Dupilumab (Dupixent™, Sanofi-Regeneron) is a monoclonal antibody against interleukin-4 receptor alpha that has been evaluated as a novel systemic therapy for moderate-to-severe atopic dermatitis in adults.[10] Dupilumab may provide an important therapeutic option for many patients with moderate-to-severe atopic dermatitis who have not had an adequate response to treatment. Key trials for dupilumab included patients >18 years old with moderate-to-severe atopic dermatitis with an Investigator's Global Assessment (IGA) score of 3 or 4, an EASI ≥ 16 at baseline, and involvement of at least 10% of the body surface area, for whom topical treatment provided inadequate control or was medically inadvisable.[10] In these trials, dupilumab consistently met prespecified Investigator's Global Assessment targets representing successful outcomes in 30-44% of patients, compared to 2-12% for placebo, as well as substantially increasing the likelihood of achieving EASI 75

compared to placebo. The long-term health outcomes of dupilumab have yet to be assessed, though it is believed to be more targeted and safer than existing systemic therapies.

Most traditional atopic dermatitis treatments such as moisturizers and emollients have little to no cost to the health care system, and low costs to the patient or family. Dupilumab, though likely more effective, is more expensive than existing treatment options. In this study, we aim to identify the cost-effectiveness of dupilumab compared to usual care in adults with moderate-to-severe atopic dermatitis.

METHODS

This model compared dupilumab (300 mg dosed every two weeks after a 600-mg loading dose) and usual care with emollients.

Target Population

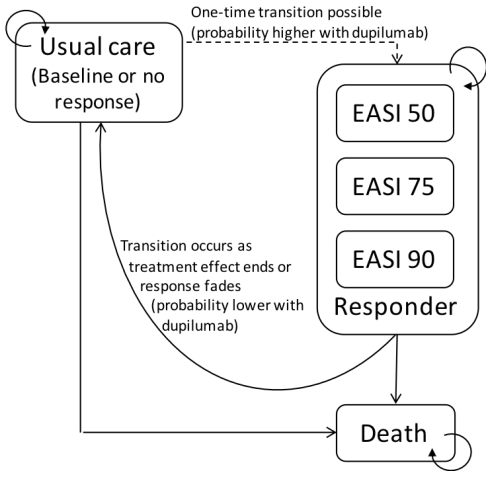
The target population for this model was adults in the United States with moderate-to-severe atopic dermatitis inadequately controlled with topical therapy, or for whom topical therapies were medically inadvisable. For the base case analysis, we assumed 53% of patients had moderate disease (defined as IGA), and the remaining 47% had severe disease (IGA4).[11] We additionally examined subpopulations of moderate and severe patients separately. The modeled population had a mean age of 38 years and was 53% male.[12]

The model does not explicitly evaluate patients with common comorbidities such as asthma, with different levels of adherence to emollients, or with varying atopic dermatitis complications such as skin infections. However, the trial populations upon which the model and clinical inputs were derived included these patients; therefore, the effects of dupilumab treatment on these patients is captured at the population level.

Model Structure

We developed a Markov model in Microsoft Excel with health states categorized by treatment response. Treatment response was defined by the percent decrease in Eczema Area and Severity Index (EASI) score after a patient began treatment (either dupilumab or usual care): at least a 50% decrease (EASI 50), a ≥75% decrease (EASI 75), a ≥90% decrease (EASI 90), or no response (Figure 1). The model estimated the time spent in each of these health states using 4-month cycles over a lifetime horizon. All patients entered the model in the non-responder state and could then transition to responder states one cycle after beginning treatment. In subsequent cycles, patients could transition from any responder state to the non-responder state, and from any state to death. Patients could not transition between EASI 50, 75, and 90 responder categories. Time spent in each health state was weighted for quality-of-life to calculated quality adjusted life-years (QALYs).

FIGURE 1. Markov model structure.



Clinical Probabilities

Treatment effectiveness was modelled by the probability of entering the EASI 50, EASI 75, and EASI 90 states after initiating treatment (Table 1).[13] Patients who responded to dupilumab transitioned from all three responder health states back to the non-responder state as they discontinued dupilumab, at a rate of 6.3% annually.[13] Patients on usual care who were responders transitioned to non-response at a rate equivalent to recurrence rate for usual care populations in trials, 65.8% every 16 weeks.[14]

Patients transitioned to death according to U.S. age-dependent general population mortality rates weighted by gender.[15] We assumed that treatment for atopic dermatitis and dupilumab had no impact on mortality.

Quality-of-Life

Utility values for quality-of-life and costs were applied to each health state (Table 2).[13] Utility values were collected in the dupilumab clinical trials using the EQ-5D. Utilities were collected at baseline and 16 weeks for three clinical trials, and were consistent across the three trials.[13] We assumed that utility values in the 'no response' health state were equivalent for patients who never had a response and for those who transitioned back to the no response state after an initial response.

Costs

For the cost of dupilumab, we used the annual list price of $37,000 for 300 mg dosed every two weeks. According to the manufacturer, the average net price in the US market would be no more than $31,000.[13] We present results here using the list price and the estimated net price. We assumed compliance of 95.2% in the first cycle and 98.6% thereafter based on the observed compliance in the clinical trials.[13] We also applied a cost of $20 for one-time self-injection training (CPT 992110).[16]

TABLE 1.

Percentage of Patients With Moderate and Severe Baseline Disease in Each Mutually Exclusive EASI Response Category

EASI Category	% of Moderate Patients in Each Category Following Initial Response[13]		% of Severe Patients in Each Category Following Initial Response13	
	Usual care	Dupilumab	Usual care	Dupilumab
Baseline/No response	70.30%	25.40%	81.90%	38.30%
EASI 50	12.00%	16.00%	9.80%	24.10%
EASI 75	8.30%	17.60%	3.90%	14.20%
EASI 90	9.40%	41.00%	4.30%	23.30%

For all patients in the model, we applied an annual cost of other healthcare (exclusive of drug costs), which included all direct costs of care such as doctor visits and hospitalizations. These costs were based on an analysis of Truven Health Marketscan® Commercial Claims and Encounters database during 2013 for patients with a diagnosis of atopic dermatitis. Though we did not link costs to specific health events or outcomes, in general these costs include all costs of care for atopic dermatitis patients, including costs from non-adherence, or from treating infections or comorbidities such as asthma. The non-responder/usual care health state had a baseline annual cost of $11,630 (standard error $683), based on the annual cost for patients with atopic dermatitis treated with phototherapy or who were prescribed any systemic immunomodulatory medications used for this disease (i.e., prednisone, cyclosporine, methotrexate, azathioprine or mycophenolate) minus prescription drug costs.[13] Responder categories had a lower annual cost of $7,346 (standard error $25,187), based on the annual cost (minus prescription drug costs) for patients with atopic dermatitis who did not have phototherapy or systemic immunomodulatory medications.[13] This cost was the same for all three responder states. We used a US health system perspective. All costs are presented in 2017 US dollars.

Adverse Events

We included three adverse events associated with dupilumab use based on clinical trial data (Table 3). For each adverse event, we applied an associated cost and disutility.

TABLE 2.

Quality of Life Utility Values Representing Patients' Quality of Life at Baseline or With No Response and in Responder Categories EASI 50, EASI 75, and EASI 90

EASI Category	Utility for Moderate Patients[13]	Utility for Severe Patients[13]
Baseline/No response	0.684	0.535
EASI 50	0.892	0.882
EASI 75	0.893	0.890
EASI 90	0.907	0.911

Analysis

We summed QALYs and total costs over the remaining lifetime of the patients. We also calculated the incremental cost-effectiveness ratio (ICER), the marginal cost for one additional QALY from treatment with dupilumab compared to usual care. We used a 3% discount rate for costs and QALYs.

We completed a one-way sensitivity analysis to identify key drivers of the model. We also conducted a probabilistic sensitivity analysis by jointly varying all model parameters over 5,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. We used normal distributions for age, gender, severity, and dupilumab costs; beta distributions for utilities, initial transition probabilities, probabilities, and rates; and gamma distributions for non-drug costs; all parameterized using standard errors or expected ranges. We used the probabilistic results to calculate the probability that dupilumab would be cost effective compared to usual care at a range of willingness-to-pay thresholds.

RESULTS

For the base case population (combined moderate and severe patients), dupilumab provided an additional 1.91 QALYs over the remaining lifetime of a patient. Total discounted lifetime cost for patients treated with dupilumab was projected to be $509,600 using the list price for dupilumab, and $466,200 using the net price, including $267,800 (list) or $224,300 (net) for dupilumab drug costs, as well as $241,800 in other healthcare costs (Table 4). Total discounted lifetime cost for usual care patients was projected to be $271,500. This led to an ICER of $124,500/QALY or $101,800/QALY using the list or net price, respectively (Table 4).

For patients with moderate atopic dermatitis QALYS were higher due to better quality of life (17.62 for dupilumab and 16.00 for usual care). Other healthcare costs were slightly lower ($239,000 for dupilumab and $271,400 for usual care), but dupilumab costs were higher ($291,000 or $243,800 for list or net price) because patients remained on dupilumab longer (Table 4). This led to a higher ICER of $160,000/QALY or $130,800/QALY using the list or net price, respectively. For patients with severe atopic dermatitis, QALYS were lower due to worse quality

TABLE 3.

Adverse Events Included in the Model				
Adverse Event	**Rate: Dupilumab[13]**	**Rate: Usual care[13]**	**Cost[13]**	**Disutility**
Injection site reaction, one-time	11.00%	--	$108.13	0.004[17]
Allergic conjunctivitis, per cycle	3.00%	0.90%	$73.40	0.03[18] (*rhinoconjunctivitis*)
Infectious conjunctivitis, per cycle	4.30%	0.70%	$138.82	0.03[18] (*rhinoconjunctivitis*)

of life (14.77 for dupilumab and 12.52 for usual care). Other healthcare costs were slightly higher ($244,900 for dupilumab and $271,600 for usual care), but dupilumab costs were lower ($241,700 or $202,500 for list or net price) because patients remained on dupilumab for a shorter time (Table 4). This led to a lower ICER of $95,800/QALY or $78,300/QALY using the list or net price, respectively.

Key drivers of the model results were utility values for quality-of-life for non-responders, and the price of dupilumab (Figure 2). For patients with moderate atopic dermatitis, the utility value for moderate atopic dermatitis with EASI 90 and EASI 75 were key drivers of the results. For patients with severe atopic dermatitis, the utility value for severe patients with EASI 50 and EASI 90 were key drivers of the results.

The 95% credible range for incremental QALYs for dupilumab compared to usual care in the base case was 1.24-1.91, and for costs was $135,800-$219,200 using the list price for dupilumab and $104,500-$173,400 using the net price for dupilumab (Figure 3), which corresponded to an ICER range of $66,400-$116,400/QALY and $51,000-$92,600/QALY, respectively. At willingness-to-pay thresholds of $50,000/QALY, $100,000/QALY, and $150,000/QALY for the base case population, dupilumab had a 1%, 30%, and 77% probability of being cost-effective compared to usual care, respectively, using the list price for dupilumab (Figure 4). Using the net price, these probabilities increased to 2%, 59%, and 88%.

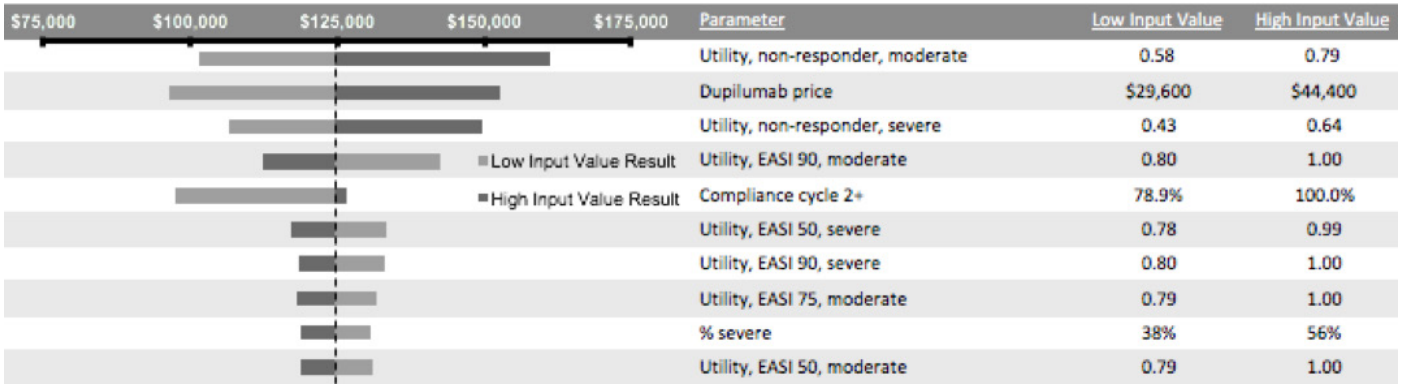
DISCUSSION

We performed an evaluation of the use of dupilumab versus usual care for patients with moderate-to-severe atopic

TABLE 4.

Results for the Base Case (Combined Moderate And Severe) Population, Moderate Patients Only, and Severe Patients Only			
Outcome	**Usual Care**	**Dupilumab Using List/Net Price**	**Incremental Using List/Net Price**
Base case population			
Total Costs	$271,461	$509,593/$466,168	$238,132/$194,708
Drug Costs	--	$267,797/$224,372	$267,797/$224,372
Other Healthcare Costs	$271,461	$241,796	($29,665)
QALYs	14.37	16.28	1.91
Cost per Additional QALY	--	--	$124,541/$101,830
Moderate population			
Total Costs	$271,356	$530,044/$482,861	$258,688/$211,506
Drug Costs	--	$290,969/$243,786	$290,969/$243,786
Other Healthcare Costs	$271,356	$239,075	($32,281)
QALYs	16	17.62	1.62
Cost per Additional QALY	--	--	$159,988/$130,807
Severe population			
Total Costs	$271,579	$486,532/$447,344	$214,953/$175,765
Drug Costs	--	$241,668/$202,480	$241,668/$202,480
Other Healthcare Costs	$271,579	$244,864	($26,715)
QALYs	12.52	14.77	2.24
Cost per Additional QALY	--	--	$95,751/$78,295

FIGURE 2. Results of one-way sensitivity analysis: ICERs for base case population when input parameters are varied.



Parameter	Low Input Value	High Input Value
Utility, non-responder, moderate	0.58	0.79
Dupilumab price	$29,600	$44,400
Utility, non-responder, severe	0.43	0.64
Utility, EASI 90, moderate	0.80	1.00
Compliance cycle 2+	78.9%	100.0%
Utility, EASI 50, severe	0.78	0.99
Utility, EASI 90, severe	0.80	1.00
Utility, EASI 75, moderate	0.79	1.00
% severe	38%	56%
Utility, EASI 50, moderate	0.79	1.00

FIGURE 3. Results of probabilistic sensitivity analysis: incremental QALYs versus incremental costs for dupilumab compared to usual care for the base case population using the list price and net price for dupilumab.

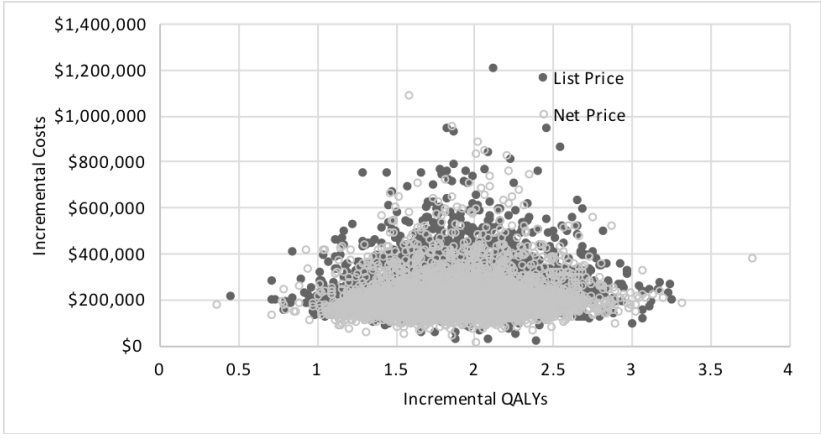
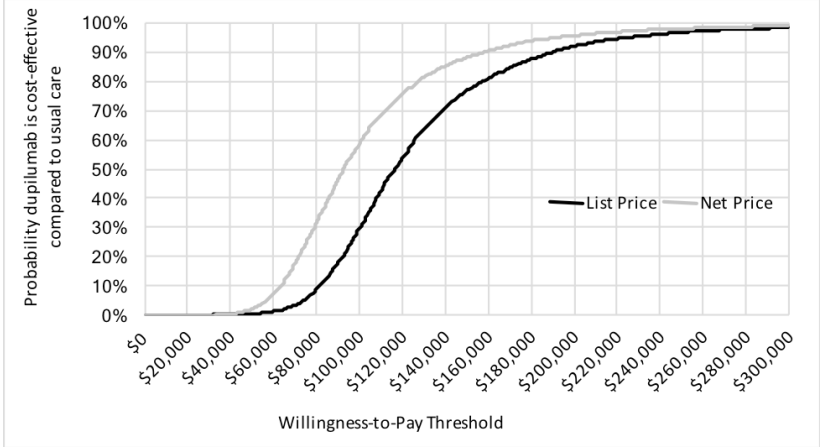


FIGURE 4. Results of probabilistic sensitivity analysis: probability that dupilumab is cost-effective compared to usual care in the base case population at a range of willingness-to-pay thresholds using the list price and net price for dupilumab.



dermatitis. We found that over the remaining lifetime of a patient, treatment with dupilumab would provide 1.91 additional QALYs, while costing an additional $194,700 to $238,100 (depending on the dupilumab cost source used). This yields an ICER of $124,500/QALY using the list price for dupilumab and $101,800/QALY using the net price for dupilumab, both of

which would be considered cost-effective at a willingness to pay threshold of $150,000/QALY.

Health care payers may desire to implement policies that segment their atopic dermatitis populations by severity. We found that for patients with moderate atopic dermatitis, dupilumab would provide comparably less value, with an ICER of $130,800-160,000/QALY, and for patients with severe atopic dermatitis, dupilumab would provide greater value at an ICER of $78,300-95,800/QALY. However, both groups would still be under the $150,000 threshold using the net price estimates. Patients with moderate atopic dermatitis were more likely to respond to dupilumab treatment; therefore, the average time patients spent on drug was longer, leading to higher average dupilumab drug costs. There is an associated cost offset while on treatment, so their average non-drug health care costs were lower. Still, the higher net cost led to a larger incremental cost, and hence a larger ICER compared to patients with severe atopic dermatitis. For patients with severe atopic dermatitis, because the baseline utility value was lower, the utility improvement when treated with dupilumab was higher. That led to a larger incremental QALY benefit, and hence a smaller ICER relative to the patients with moderate atopic dermatitis. Despite the different ICER estimates, a value-based approach to reimbursement using a $150,000 threshold would not lead to different reimbursement policies based on severity at presentation.

Throughout the original study process, a collaborative relationship with the manufacturer in obtaining key model estimates pertaining to drug trial data and costs led to a more accurate economic evaluation that will be more useful in real-world practice for patients and providers as well as payers. Additionally, as dupilumab was a new product at the time of study, the manufacturer had the opportunity to align the list price and rebate structure with a value based price, which could lead to quick and relatively smooth access to their drug for patients in need.[19] This process could lead to improved outcomes for patients, the manufacturer, potential payers, and the researchers. We believe this type of collaborative process can be advantageous for policy makers, researchers and manufacturers across various therapeutic areas.

There were several key limitations of our analysis. First, there were limited data for health outcomes for patients with atopic dermatitis over long periods of time, particularly for sustained response or discontinuation rates. Second, there were limited data on costs of atopic dermatitis, particularly stratified by severity. Ideally, we would have direct medical treatment costs as well as productivity loss costs stratified by EASI category. In the absence of these data, we used a total annual cost of direct medical care stratified only by responder versus non-responder. However, varying the cost of other healthcare treatment did not substantially impact our conclusions. Finally, atopic dermatitis is a heterogeneous condition and patients experience a wide range of symptoms and severities that are difficult to include in a single model.

Dupilumab was projected to be more cost-effective in patients with severe atopic dermatitis, but even in patients with moderate atopic dermatitis, the ICER remained close to the upper range of commonly cited thresholds. We found that dupilumab improves health outcomes compared to usual care, but with additional costs. At the net price or list price of dupilumab, this is likely a cost-effective intervention.

DISCLOSURES

The authors have no disclosures or conflicts of interest to report.

REFERENCES

1. Shaw TE, Currie GP, Koudelka CW, Simpson EL. Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. *J Invest Dermatol*. 2011;131(1):67-73.
2. Silverberg JI, Hanifin JM. Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. *J Allery Clin Immunol*. 2013;132(5):1132-1138.
3. Silverberg JI, Garg NK, Paller AS, Fishbein AB, Zee PC. Sleep disturbances in adults with eczema are associated with impaired overall health: a US population-based study. *J Invest Dermatol*. 2015;135(1):56-66.
4. Holm JG, Agner T, Clausen ML, Thomsen SF. Quality of life and disease severity in patients with atopic dermatitis. *J Eur Acad Dermatol Venereol*. 2016;30(10):1760-1767.
5. Yu SH, Attarian H, Zee P, Silverberg JI. Burden of Sleep and Fatigue in US Adults With Atopic Dermatitis. Dermatitis: contact, atopic, occupational, drug. 2016;27(2):50-58.
6. Weidinger S, Novak N. Atopic dermatitis. *Lancet* (London, England). 2016;387(10023):1109-1122.
7. Katz HI, Prawer SE, Mooney JJ, Samson CR. Preatrophy: covert sign of thinned skin. *J Am Acad Dermatol*. 1989;20(5 Pt 1):731-735.
8. Furue M, Terao H, Rikihisa W, et al. Clinical dose and adverse effects of topical steroids in daily management of atopic dermatitis. *Br J Dermatol*. 2003;148(1):128-133.
9. Lam LH, Sugarman JL. Adrenal Suppression With Chronic Topical Corticosteroid Use in Psoriasis Patients. *J Drugs Dermatol*. 2016;15(8):945-948.
10. Simpson EL, Bieber T, Guttman-Yassky E, et al. Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis. *New Engl J Med*. 2016;375(24):2335-2348.
11. Thaci D, Chambers C, Sidhu M, Dorsch B, Ehlken B, Fuchs S. Twice-weekly treatment with tacrolimus 0.03% ointment in children with atopic dermatitis: clinical efficacy and economic impact over 12 months. *J Eur Acad Dermatol Venereol*. 2010;24(9):1040-1046.
12. Beck LA, Thaçi D, Hamilton JD, et al. Dupilumab Treatment in Adults with Moderate-to-Severe Atopic Dermatitis. *New Engl J Med*. 2014;371(2):130-139.
13. Sanofi-Regeneron. Data on file.
14. Peserico A, Stadtler G, Sebastian M, Fernandez RS, Vick K, Bieber T. Reduction of relapses of atopic dermatitis with methylprednisolone aceponate cream twice weekly in addition to maintenance treatment with emollient: a multicentre, randomized, double-blind, controlled study. *Br J Dermatol*. 2008;158(4):801-807.
15. CDC/NCHS National Vital Statistics System. Life table for the total population: United States, 2011.
16. Center for Medicare and Medicaid Services. 2017 National Physician Fee Schedule Relative Value File January Release. 2017.
17. Boye KS, Matza LS, Walter KN, Van Brunt K, Palsgrove AC, Tynan A. Utilities and disutilities for attributes of injectable treatments for type 2 diabetes. *Eur J Health Econ*. 2011;12(3):219-230.
18. Poole CD, Bannister CA, Andreasen JN, Andersen JS, Currie CJ. Estimation of health-related utility (EQ-5D index) in subjects with seasonal allergic rhinoconjunctivitis to evaluate health gain associated with sublingual grass allergen immunotherapy. *Health Qual Life Outcomes*. 2014;12:99.

19. David M RInd DAO, Rcik Chapman, Sonya Khan, Varun Kumar, Shanshan Liu, Margaret Webb, Steven D Pearson, Josh Carlson, Marita Zimmermann. Dupilumab and Crisaborole for Atopic Dermatitis: Effectiveness and Value. Midwest CEPAC. 2017.

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